WORKSHEET for Evidence-Based Review of Science for Veterinary CPCR

1. Basic Demographics

Worksheet author(s)

Benjamin M. O'Kelley	**Date Submitted for review:**

[redacted]

2. Clinical question:

In dogs and cats with ROSC after cardiac arrest (P), does the administration of corticosteroids (I) compared to standard care (C), result in improved outcome (O) (survival to discharge, neurological outcome)?

3. Conflict of interest specific to this question:

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet?
No

4. Search strategy (including electronic databases searched):

4a. Databases

-Medline via Pubmed (1950 to June 11, 2011) – (performed on June 10, 2011)

1. "(steroids OR corticosteroids OR hydrocortisone OR dexamethasone OR prednisone OR methylprednisone) AND post cardiac arrest" [MeSH terms] - 43 hits
2. "(steroids OR corticosteroids OR hydrocortisone OR dexamethasone OR prednisone OR methylprednisone) AND following ROSC" [MeSH terms] -2 additional hits
3. "(steroids OR corticosteroids OR hydrocortisone OR dexamethasone OR prednisone OR methylprednisone) AND following cardiac arrest" [MeSH terms] – 1 additional hit
4. "(ROSC OR post cardiac arrest) AND adrenal insufficiency" [MeSH terms] – 8 additional hits
5. "CPR dog AND (steroids OR corticosteroids)" [MeSH terms] – 5 additional hits
6. "CPR cat AND (steroids OR corticosteroids)" [MeSH terms] – 3 additional hits
7. "CPR AND (dog OR cat) AND adrenal insufficiency" [MeSH terms] – no additional hits
8. "(CPR OR post arrest OR ROSC) AND (critical illness related corticosteroid insufficiency OR CIRCI)" – no additional hits

-CAB Abstracts:
Search using the same terms as for Medline yielded no additional hits

4b. Other sources

-Cochrane Database
-Forward searching from references obtained via articles above
-Searching references from veterinary CPR literature
These sources yielded no new hits addressing the clinical question

4c. State inclusion and exclusion criteria for choosing studies and list number of studies excluded per criterion

Inclusion criteria
-Articles in English language

Exclusion criteria
-Steroids give pre-arrest or during CPR rather than post-arrest
-Articles discussing or documenting adrenal insufficiency and/or changes in hypothalamic-pituitary-adrenal axis function, but not directly assessing the effect of steroid administration
-Abstracts only
-Editorials
-Articles in languages other than English

4d. Number of articles/sources meeting criteria for further review:
Five sources from fulfilled the criteria for further review
-One research study using dogs (Ebmeyer et al 2000)
-One research study using rats (Katz et al 1989)
-One prospective randomized controlled clinical trial (Mentzelopoulos et al 2009)
-Two retrospective studies in human patients (Grafton and Longstreth 1988, Jastremski et al 1989)

5. Summary of evidence

Evidence Supporting Clinical Question

Good						
Fair						
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Neutral to Clinical question

Good						
Fair						*Mentzelopoulos 2009* *D,E=organ failure-free days, higher MAP, higher ScvO2* *Jastremski 1989* *D* *Grafton* *1988* *CD* *Katz* *1989* *E=decreased pathologic changes in brain enzymes, return of EEG activity, norepinephrine requirement*
Poor			Ebmeyer 2000 E= neurologic performance in first 96 hrs post-ROSC and brain histologic changes at 96 hrs			
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

Evidence Opposing Clinical Question

Good						
Fair						
Poor						
	1	**2**	**3**	**4**	**5**	**6**
Level of evidence (P)						

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Non-target species studies

6. REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

An evidenced-based evaluation of the effect of corticosteroids administered following ROSC yields no clinical studies using dogs or cats. Only one research study using dogs is identified, and no research studies using cats are identified. The majority of publications located using the search terms listed in section 4a above are excluded because they merely discuss or document alterations in HPA axis function following ROSC from cardiopulmonary arrest but do not evaluate intervention. While there seems to be evidence that HPA axis dysfunction and "relative adrenal insufficiency" *may* occur in some animals and humans post-ROSC, the effects of standard administration of glucocorticoids post-ROSC have not been effectively studied.

The single research study using dogs (Ebmeyer et al 2000) evaluated a combination of treatments, leaving the "control" group inadequate to evaluate specifically the effects of methylprednisone (MP) administered following cardiac arrest. Post-ROSC neurologic function was measured through assignment of a "neurologic deficit score," (NDS) ranging from 0% (normal) to 100% (brain death) and "overall performance categories," (OPC of 1-5, with 1 = normal, 2 = moderate disability, 3 = severe disability, 4 = coma and 5 = death) every 6-8 hours for 96 hours following ROSC. At 96 hours, dogs were euthanized and histologic brain damage scores (HDS) were recorded. Of the four groups (6 dogs each), one group received thiopental 90 mg/kg and one group was given thiopental 30 mg/kg, methylprednisolone 130 mg/kg and phenytoin 15 mg/kg following ROSC. The group receiving methyprednisolone was the only group in which all 6 dogs achieved OPC of 1 or 2. This group also had the best NDS and HDS, but it was impossible to determine whether or not these improved outcomes were caused by the methylprednisolone, the lower dose of thiopental, or the phenytoin.

The research study evaluating the effect of post-ROSC steroid administration on brain enzyme changes in rats featured four groups, each including 5 rats, who were asphyxiated under anesthesia to induce pulselessness. After 10 minutes of asphyxia (typically 7 minutes of cardiac arrest), the rats were resuscitated using a standardized protocol. Rats two of the groups received no steroids, and rats in one group were given methylprednisolone (MP) 30 mg/kg 20 minutes prior to asphyxiation. The final group of 5 rats were given MP 30 mg/kg immediately upon ROSC. Researchers identified a trend towards less changes in lysosomal brain enzymes in the rats who received MP, but this trend failed to reach statistical significance. Even if the changes would have reached significance, the importance of this on clinically relevant outcomes (survival to hospital discharge, long-term neurologic performance) is unknown in clinical canine and feline patients. There is no statistical significance or evidenced-based conclusions that can be drawn from the research group's observation that rats receiving MP experienced EEG activity at 20 minutes post-ROSC (whereas rats who did not receive MP did not experience EEG activity at this time point) and required no post-ROSC norepinephrine. Statistical significance of this observation was not determined, and the study was not designed to study the effects of MP on norepinephrine requirements.

Two human clinical studies have retrospectively evaluated the effect of corticosteroids administered post-ROSC. Grafton and Longstreth retrospectively evaluated 458 consecutive patients admitted to the hospital following ROSC from cardiac arrest. The decision whether or not to administer steroids was left entirely in the hands of the attending physician, and the specific steroid (e.g. dexamethasone, methylprednisolone, etc), dosage and timing of administration varied. Outcomes investigated were "awakening" (regaining of consciousness) and survival to hospital discharge. No statistically significant effect of steroid administration was identified, but this retrospective study was not properly structured to investigate the effects of glucocorticoid administration post-ROSC. Instead, the authors were merely searching for an association to justify a potentially expensive prospective, randomized clinical study evaluating the effects of glucocorticoids in this patient population.

Jastremski et al retrospectively analyzed the database of the Brain Resuscitation Clinical Trial 1 Study Group to check for any association between glucocorticoid administration and outcome. No statistically significant

effect on survival or "recovery of cerebral function" (determined by the best "Cerebral Performance Category" at any time point over a one year span) could be determined. The "Brain Resuscitation Clinical Trial 1" prospective study was initially done to study the effect of thiopental on outcome in human patients who experienced an ROSC following cardiac arrest and remained comatose 10-50 minutes following ROSC. The decision whether or not to administer glucocorticoids was left to the discretion of the attending clinician because no consensus on corticosteroid use could be reached during the planning/design phase of the study.

Mentzelopoulos et al designed and executed a prospective, randomized, double-blinded, placebo-controlled, parallel-group trial in human patients experiencing in-hospital cardiac arrest from causes other than exsanguination. The study was conducted on patients who exhibited "refractory cardiac arrest," defined as (1) pulseless electrical activity, (2) asystole, or (3) pulseless ventricular tachycardia or ventricular fibrillation that failed to convert following 2-3 minutes of CPR and one monophasic external defibrillation attempt (360 J). The study compared two groups; the control group received a standardized resuscitation using repeated doses of epinephrine and placebo every 2-3 minutes until ROSC or CPR efforts were terminated. The study group received an initial dose of epinephrine, vasopressin and methylprednisone followed by repeated doses of epinephrine and vasopressin every 2-3 minutes until ROSC or CPR efforts were terminated. Four hours following ROSC, study group patients experiencing "post-resuscitation shock" (defined as "new postarrest circulatory failure or postarrest need for at least a 50% increase in any prearrest vasopressor/inotropic support targeted to maintain mean arterial pressure above 70 mm Hg) began a continuous infusion of 300 mg hydrocortisone/day. Control group patients exhibiting post-resuscitation shock began a placebo infusion. Hydrocortisone dose was weaned by decreasing to 200 mg/day on the day that vasopressor support was no longer needed *or* 8 days after cardiac arrest (whichever occurred first), then decreasing to 100 mg/day on the following day, then discontinuing hydrocortisone (or placebo) on the next day. Primary endpoints were ROSC lasting 15 minutes or longer and survival to hospital discharge. Other endpoints that were analyzed included central venous oxygen saturation, MAP, "organ failure-free days," and measurement of cytokines (TNF-α, IL-1β, IL-6, IL-8 and IL-10).

This study achieved some improved outcomes, including increased ROSC and survival to hospital discharge, and these outcomes were statistically significant. The portion of this study that is relevant to post-ROSC steroid administration was the treatment of patients with post-resuscitation shock (hydrocortisone vs. placebo). Study group patients, who all received hydrocortisone if they exhibited post-resuscitation shock, exhibited a statistically significantly improved MAP and increased ScvO2, and a trend towards more organ failure-free days. Most importantly, study group patients with post-resuscitation shock had statistically significant increased survival to hospital discharge. None of the 15 patients in the control group who experienced post-resuscitation shock survived to hospital discharge, but 8 of the 27 patients in the study group survived to hospital discharge. The authors noted a 6.7-fold reduction of risk of death in patients with post-resuscitation shock if they were treated with hydrocortisone versus placebo.

The main problem with interpretation of the effect of hydrocortisone in the post-resuscitation shock group is that this group had a different initial resuscitation than the control group. It is not possible to determine whether the increased survival in the study group was caused by the post-ROSC hydrocortisone, or if it related to improved hemodynamics observed immediately following ROSC. In other words, the improved outcome could have been related to less injury occurring due to immediate (prior to post-ROSC steroid administration) hypoperfusion. In summary, while the study did find an improvement in patients resuscitated with epinephrine-vasopressin-methylprednisolone and subsequently treated for post-resuscitation shock using hydrocortisone, this improvement cannot be proven to be due to post-resuscitation steroid administration alone.

7. Conclusion

One research study using dogs (Ebmeyer et al 2000) and one prospective randomized human clinical trial (Mentzelopoulos 2009) have found some beneficial effects of specific, multifaceted resuscitation protocols including post-resuscitation corticosteroid administration, but there is not sufficient evidence that the beneficial outcomes were caused specifically by the corticosteroid administration. A rat model (Katz 1989) found no evidence to support or refute routine post-ROSC corticosteroid administration. Two retrospective studies in human patients (Grafton and Longstreth 1988, Jastremski 1989) failed to identify any association between post-ROSC corticosteroid administration and relevant changes in outcome. Because neither of these retrospective studies was properly designed to investigate the clinical question at hand, recommendations for (or against) routine administration of post-ROSC corticosteroid administration cannot be made based on these studies.
Given the presence of evidence of alterations to the HPA axis in some humans and animals following ROSC, as well as some evidence of improved outcomes utilizing multifaceted resuscitation protocols including post-ROSC corticosteroid administration, the use of corticosteroids following ROSC should be further investigated.

DISCLAIMER: Potential possible wording for a Consensus on Science Statement. Final wording will differ due to other input and discussion.
CONSENSUS ON SCIENCE: Evidence from one research study in dogs, one research study using rats, one prospective, randomized double-blinded clinical trial in human patients, and two retrospective human studies document no evidence of improved or reduction in survival to hospital discharge or neurologic outcome when corticosteroid administration is added to standard post-ROSC treatment.
While post-ROSC corticosteroid administration may be considered, routine post-ROSC corticosteroid administration in dogs and cats cannot be recommended.

8. Acknowledgement

Nil

9. Citation list

Ebmeyer, U et al (2000). “Thiopental combination treatments for cerebral resuscitation after prolonged cardiac arrest in dogs. Exploratory outcome study.” Resuscitation 45(2);119-131.

Abstract

We postulate that mitigating the multifactorial pathogenesis of postischemic encephalopathy requires multifaceted treatments. In preparation for expensive definitive studies, we are reporting here the results of small exploratory series, compared with historic controls with the same model. We hypothesized that the brain damage mitigating effect of mild hypothermia after cardiac arrest can be enhanced with thiopental loading, and even more so with the further addition of phenytoin and methylprednisolone. Twenty-four dogs (four groups of six dogs each) received VF 12.5 min no-flow, reversed with brief cardiopulmonary bypass (CPB), controlled ventilation to 20 h, and intensive care to 96 h. Group 1 with normothermia throughout and randomized group 2 with mild hypothermia (from reperfusion to 2 h) were controls. Then, group 3 received in addition, thiopental 90 mg/kg i.v. over the first 6 h. Then, group 4 received, in addition to group 2 treatment, thiopental 30 mg/kg i.v. over the first 90 min (because the larger dose had produced cardiopulmonary complications), plus phenytoin 15 mg/kg i.v. at 15 min after reperfusion, and methylprednisolone 130 mg/kg i.v. over 20 h. All dogs survived. Best overall performance categories (OPC) achieved (OPC 1 = normal, OPC 5 = brain death) were better in group 2 than group 1 (< 0.05) and numerically better in groups 3 or 4 than in groups 1 or 2. Good cerebral outcome (OPC 1 or 2) was achieved by all six dogs only in group 4 (P < 0.05 group 4 vs. 2). Best NDS were 44 +/- 3% in group 1; 20 +/- 14% in group 2 (P = 0.002); 21 +/- 15% in group 3 (NS vs. group 2); and 7 +/- 8% in group 4 (P = 0.08 vs. group 2). Total brain histologic damage scores (HDS) at 96 h were

156 +/- 38 in group 1; 81 +/- 12 in group 2 (P < 0.001 vs. group 1); 53 +/- 25 in group 3 (P = 0.02 vs. group 2); and 48 +/- 5 in group 4 (P = 0.02 vs. group 2). We conclude that after prolonged cardiac arrest, the already established brain damage mitigating effect of mild immediate postarrest hypothermia might be enhanced by thiopental, and perhaps then further enhanced by adding phenytoin and methylprednisolone.

Comments:

LOE 3 (experimental study in dogs).
While the overall quality would be good due to the presence of control groups, the quality of the study design for specifically evaluating the effect of corticosteroid administration post-ROSC is poor.
Neutral for steroid use.
Funded in part by A.S. Laerdal Foundation and the US Navy Medical Research and Development Command.
Investigated the effects of a post-ROSC treatment protocol including mild hypothermia, thiopental, phenytoin and methylprednisolone (MP). Included four groups, with group #4 (receiving the entire protocol above) showing some improvements in neurologic function when compared with other groups. A control group receiving all treatments except MP was not included, so the specific effect of MP cannot be determined.

Grafton, ST and Longstreth WT (1988). "Steroids after cardiac arrest: a retrospective study with concurrent, nonrandomized controls." Neurology 38(8):1315-1316.

Abstract

We retrospectively examined the effect of steroid treatment on the outcome of 458 consecutive patients admitted after out-of-hospital cardiac arrest. Of those given steroids, 128/213 (60%) regained consciousness, and of those not given steroids, 150/245 (61%) regained consciousness. Findings remained unchanged using logistic regression to adjust for differences in the two treatment groups. These results suggest that there is no role for steroids in the treatment of global brain ischemia.

Comments:

LOE 6 (retrospective study in human patients).
Quality = fair (compared treatment group against non-randomized control group).
Neutral for steroid use.
No industry funding.
Evaluated 459 consecutive patients hospitalized following out-of-hospital cardiac arrest and subsequent ROSC. Failed to detect a difference in "awakening" or survival to hospital discharge in patients who received steroids vs. those who did not. The specific steroid, dosage and timing were not controlled.

Katz et al (1989). "Brain enzyme changes as markers of brain damage in rat cardiac arrest model. Effects of corticosteroid therapy." Resuscitation 17(1):39-53.

Abstract:

Apneic asphyxia to cardiac arrest (CA) in rats of 10 min was reversed by cardiopulmonary resuscitation (CPR), and after controlled ventilation and controlled normotension for 20 min, was followed by decapitation and brain freezing, and determination of brain concentrations of cytosolic and lysosomal enzymes. Normal values came from a control group of 10 rats without CA. In 20 rats with CA brain cytosolic enzymes CK, LD, and ASAT decreased post-arrest, while lysosomal enzyme changes were variable (Table I). Brain lactate increased 8-10-fold post-CA. To test the model, effect of methylprednisolone (MP) was studied. The 20 rats with CA were divided into 4 groups: Group I, received placebo pre-CA; Group II, MP 30 mg/kg i.v. pre-CA; Group III, placebo post-CA; and Group IV, MP post-CA. The post-CA MP Group IV was the only one without norepinephrine requirement and with return of EEG activity at 20 min. Brain CK, LD, and ASAT losses post-CA were not different between groups; and showed no differences between MP groups II and IV vs. placebo Groups I and III. When comparing both pre-CA Groups (I and II) with both post-CA Groups (III and IV), post-CA CK and ASAT levels were the same, but LD was higher in the post-CA treatment group. The lysosomal enzymes acid phosphatase, mannosidase, beta-glucuronidase and hexosaminidase showed variable

concentration changes post-CA in the four groups, with a trend toward a lesser increase of some after MP or after post-treatment. Brain enzyme changes in our asphyxial CA rat model can serve as markers of brain damage. MP post-CA might enhance cardiovascular and EEG recovery, but does not seem to influence brain enzyme levels at 20 min post-CA.

Comments:
LOE 6 (research study in rats).
Quality = fair (compares treatment group with control groups).
Neutral for steroid use.
Supported by grants from the Upjohn Company and the A.S. Laerdal Foundation.
Four groups of rats were compared; one group received pre-arrest placebo, another was given pre-arrest methylprednisolone (MP), a group was given post-ROSC placebo, and a final group was given post-ROSC MP. Brain tissues were obtained at 20 minutes, and brain enzymes were analyzed. The group given post-ROSC had a trend towards less changes in lysosomal enzymes (possibly suggesting less brain damage). Investigators also noted the post-ROSC MP group was the only group not requiring norepinephrine to maintain MAP 80-100 post-ROSC. These rats were also the only ones with EEG activity at 20 minutes, but this finding was not statistically evaluated.

Jastremski, et al (1989). "Glucocorticoid treatment does not improve neurological recovery following cardiac arrest." JAMA 262(24):3427-3430.

Abstract:
Glucocorticoids are commonly given to patients with global brain ischemia, although their efficacy has not been proved. The database of the Brain Resuscitation Clinical Trial I, a multi-institutional study designed to evaluate the effect of thiopental sodium therapy on neurological outcome following brain ischemia, was used for a retrospective review of the effects of glucocorticoid treatment on neurological outcome after global brain ischemia. This study included 262 initially comatose cardiac arrest survivors who made no purposeful response to pain after restoration of spontaneous circulation. The standard treatment protocol left glucocorticoid therapy to the discretion of the hospital investigators. This resulted in four patient groups that received either no, low, medium, or high doses of glucocorticoids in the first 8 hours after arrest. Neurological outcome was scored using a modification of the Glasgow Cerebral Performance Category Scale. None of the steroid regimens statistically improved mean group survival rate or neurological recovery rate over that observed in the group that did not receive steroids. The routine clinical practice of administrating glucocorticoids after global brain ischemia may be associated with serious complications and is not justified.

Comments:
LOE 6 (retrospective evaluation of data obtained during a prospective randomized clinical trial investigating a separate clinical question).
Quality = fair (compared a non-standardized treatment group against non-treatment group in a non-randomized fashion).
Neutral for steroid use.
Initial trial was funded with government grants.
Retrospectively searched the database of a prospective clinical trial designed to investigate the benefits of post-ROSC thiopental administration. The decision to administer steroids was left to the discretion of the attending physician. Data on steroid administration after 8 hours post-ROSC was not available, but outcomes were tracked to one year post-arrest. Neither survival to hospital discharge, nor neurologic recovery rate (defined as the best "cerebral performance category scale" classification achieved at any point during the year following arrest) was significantly affected by steroid administration.

Mentzelopoulos, et al (2009). "Vasopressin, epinephrine and corticosteroids for in-hospital cardiac arrest." Arch Intern Med 169(1):15-24

Abstract:
BACKGROUND:
Animal data on cardiac arrest showed improved long-term survival with combined vasopressin-epinephrine. In cardiac arrest, cortisol levels are relatively low during and after cardiopulmonary resuscitation. We hypothesized that combined vasopressin-epinephrine and corticosteroid supplementation during and after resuscitation may improve survival in refractory in-hospital cardiac arrest.
METHODS:
We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group trial. We enrolled 100 consecutive patients with cardiac arrest requiring epinephrine according to current resuscitation guidelines. Patients received either vasopressin (20 IU per cardiopulmonary resuscitation cycle) plus epinephrine (1 mg per resuscitation cycle) (study group; n = 48) or isotonic sodium chloride solution placebo plus epinephrine (1 mg per resuscitation cycle) (control group; n = 52) for the first 5 resuscitation cycles after randomization, followed by additional epinephrine if needed. On the first resuscitation cycle, study group patients received methylprednisolone sodium succinate (40 mg) and controls received saline placebo. Postresuscitation shock was treated with stress-dose hydrocortisone sodium succinate (300 mg daily for 7 days maximum, with gradual taper) (27 patients in the study group) or saline placebo (15 patients in the control group). Primary end points were return of spontaneous circulation for 15 minutes or longer and survival to hospital discharge.
RESULTS:
Study group patients vs controls had more frequent return of spontaneous circulation (39 of 48 patients [81%] vs 27 of 52 [52%]; P = .003) and improved survival to hospital discharge (9 [19%] vs 2 [4%]; P = .02). Study group patients with postresuscitation shock vs corresponding controls had improved survival to hospital discharge (8 of 27 patients [30%] vs 0 of 15 [0%]; P = .02), improved hemodynamics and central venous oxygen saturation, and more organ failure-free days. Adverse events were similar in the 2 groups.
CONCLUSION:
In this single-center trial, combined vasopressin-epinephrine and methylprednisolone during resuscitation and stress-dose hydrocortisone in postresuscitation shock improved survival in refractory in-hospital cardiac arrest.

Comments:
LOE 6 (prospective randomized human clinical trial)
While the overall quality of the study is good (double-blinded, placebo-controlled, randomized), the quality of the study design for addressing the clinical question of whether or not corticosteroid use is helpful following ROSC was fair at best.
Neutral for steroid use.
Patients experiencing in-hospital cardiac arrest were randomized to receive standardized resuscitation utilizing first an injection of epinephrine and placebo (control group), or an epinephrine-vasopressin-methylprednisolone combination (study group). Subsequent cycles of 2-3 minutes compressions were continued, followed by assessment of rhythm and administration of either epinephrine and placebo (control group) or epinephrine and vasopressin (study group) until ROSC or cessation of CPR efforts. Patients who experienced post-ROSC shock were treated with hydrocortisone (study group) or placebo (control group). A statistically significant improvement in survival, as well as improvements in hemodynamic variables and attenuation of cytokine responses associated with systemic inflammation were all detected in the study group. The specific effects of the post-ROSC corticosteroids administration could not be detected due to failure of a proper control group receiving identical initial resuscitation but not receiving post-ROSC corticosteroid treatment.

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